REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

As indicated in the Office Action Summary, claims 1, 7, 11-15, 19, 20 and 24-32 are currently pending. Claims 1, 14 and 19 are amended herein. New claims 33-40 are added. Basis for the amendments to the claims and new claims may be found throughout the specification and claims as-filed, especially at page 24, lines 24-26, page 15, lines 35-37, page 16, lines 31-35, page 17, lines 6-11 and claim 24. Thus, no new matter is presented by way of the present Amendment.

Claims 20 and 24 are canceled herein. Applicants reserve the right to file at least one continuation or divisional application directed to any subject matter canceled by way of the present Amendment.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1, 7, 11, 12, 13, 19, 20, 24, and 25 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly failing to comply with the written description requirement. Specifically, the Examiner argues that amended claim 1, as filed on November 20, 2003, introduces new subject matter into the application with the phrase "wherein the IL-2 and MIP chemokine work together synergistically". In the interest of expediting prosecution, and without acquiescing in the rejection, Applicants have amended the claims to remove the language "wherein the compound is directly administered via a vector or a mixture of vectors expressing

both IL-2 and a MIP chemokine" and "wherein the IL-2 and MIP chemokine work together synergistically" from the claims. Thus, the rejection is moot.

Applicants submit new claims 33-40 herewith, directed to a method of treating a proliferative disease in a patient in comprising administering a composition by direct administration into an accessible tumor or at its periphery. The composition comprises a vector or a mixture of vectors comprising a nucleic acid sequence encoding all or part of a MIP chemokine or a natural variant of MIP-1αor MIP-1β, and at least one nucleic acid sequence encoding IL-2. The nucleic acid sequences are placed under the control the elements required for expression of both IL-2 and said MIP chemokine, and the IL-2 and MIP chemokine work together synergically to inhibit the growth or cause the rejection of a tumor in said patient when compared to the anti-tumor response in said patient administered with a composition comprising a vector comprising only the nucleic acid sequences.

Applicants submit that these new method claims are supported by the specification, including the subject matter directed to IL-2 and MIP chemokine working *synergistically* together. The new claims further clarify the functional role of the synergistic action of IL-2 and MIP, with the language "wherein the IL-2 and MIP chemokine work together synergically to inhibit the growth or cause the rejection of a tumor in said patient when compared to the anti-tumor response in said patient administered with a composition comprising a vector comprising only the nucleic acid sequence (i) or the nucleic acid sequence (ii)".

In the outstanding Office Action, the Examiner states the specification does not describe a synergistic effect and does not specifically point out what cytotoxic composition produces a synergistic effect. Moreover on page 10 of the Office

Action, the Examiner states that the functional language reciting the synergistic action of IL-2 and MIP is not commensurate with the scope of a product. To this end, on page 3 of the Office Action, the Examiner states that the working examples do not disclose a process using recombinant vectors comprising a nucleic acid sequence encoding an MIP chemokine and a nucleic acid sequence encoding IL-2, wherein the IL-2 and MIP chemokine work together synergically. Applicants disagree.

Example 2 shows the anti-tumor protection provided by compositions associating the action of IL-2 and a MIP chemokine in three different tumor models, B16F0 (*see* Figures 1 and 20), RENCA (*see* Figures 3 and 4) an dP815 (*see* Figures 5 and 6) respectively, as compared to the anti-tumor effect observed with individual vector encoding IL-2, MIP-1α or MIP-1β. In all of the above experiments, as set forth in the specification, the results show an improved increase in survival rates (*see* Figures 1, 3, and 5) associated with a decrease in tumor volumes (*see* Figures 2, 4, and 6), as well as in the mice treated with adenoviral vectors expressing both IL-2 and MIP chemokine as compared to the animals treated with adenoviral vectors expressing only IL-2, MIP-1α, MIP-1β or other combinations.

For example, as shown in Figure 4, 36% of mice implanted with Renca tumors were tumor-free at least 100 days after intratumoral injection of an adenoviral vector expressing both IL-2 and MIP-1β. In contrast, all animals treated with an adenoviral vector expressing MIP-1β were dead 40 days following injection and only 14% survived after administration of a recombinant vector expressing only IL-2. As shown in Figure 6, the anti-tumor protection provided by the adenoviral vector co-expressing IL-2 and MIP-1α is even more pronounced in the P815 model, because

67% of the treated mice implanted with P815 tumors were tumor-free at least 90 days after intratumoral injection.

Thus, Applicants submit that that present specification provides support for a product wherein the IL-2 and MIP chemokine work together synergistically, as well as for the claimed language regarding synergism presented herein in new claims 33-40.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1, 7, 11-13, 19, 20, 24 and 25 stand rejected under 35 U.S.C. § 112, second paragraph as purportedly indefinite for the recitation of 'the compound', as recited in independent claim 1.

Without acquiescing in the rejection, claim 1 is amended herein to remove the term "compound' and to recite the compound in structural terms. Specifically, the claimed composition comprises a vector or a mixture of vectors comprising (i) a nucleic acid sequence encoding all or part of a MIP-1α chemokine or a natural variant of MIP-1β and (ii) at least one nucleic acid sequence encoding IL-2, wherein said nucleic acid sequences (i) and (ii) are placed under the control of elements required for their expression in a host cell. As described in the Examples set forth in the present specification, the IL-2 and MIP-encoding vectors are the compound that is administered to the mammal in need of treatment. Thus, Applicants submit that in the light of the amendments and what is recited in the specification, it would be clear to the skilled artisan what is claimed with regard to the claimed compound.

Claims 1, 7, 11-13, 19, 20, 24, and 25 stand rejected as purportedly incomplete. Specifically, the Examiner argues that the claims omit the essential

structural and cooperative relationship of the IL-2 and MIP chemokine elements. As noted above, the claims have been amended herein to remove the language regarding the synergistic relationship between IL-2 and the MIP chemokine. With regard to new claims 33-40, Applicants submit the relationship between IL-2 and the MIP chemokine is clarified, based on what is set forth in the specification. Thus, Applicants submit this rejection is obviated.

Claim 20 stands rejected for the recitation of the phrase "comprising capable of being transformed into a cytotoxic molecule by a polypeptide having at least cytotoxic activity'. Claim 20 is canceled herein without prejudice or disclaimer thereto. Thus, this rejection is moot.

Rejections under 35 U.S.C. § 103

Claims 1, 7,11-13,19, 20, 24, and 25 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Boursnell et al. (U.S. Patent No. 6,287,557) as taken with Hobart et al. (U.S. Patent No. 5,147,055) and Nakashima et al. (*Phar. Res* 13:1896-1901 (1996)).

Boursnell et al. purportedly disclose virus vectors encoding nucleotide sequences expressing immunomodulating proteins including cytokines and chemokines and combinations thereof for cancer immunotherapy, wherein each of the sequences are placed under control of a known viral promoter of a mammalian specific promoter. Hobart et al. purportedly disclose a method of treating a solid tumor in an animal comprising introducing a vector comprising IL-2 into the solid tumors. Nakashima et al. purportedly disclosed reducing tumorigenicities in mice inoculated with adenocarcinoma cells using a vector comprising a nucleotide

sequence encoding MIP-1α. Nakashima et al. purportedly disclose that MIP-1α has potential value for cancer gene therapy. The Examiner argues that it would have been obvious to the skilled artisan to combine the discloser of Boursnell et al. taken with Hobart et al. and Nakashima et al. to make and use a composition comprising a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding an MIP chemokine. Applicants traverse.

As set forth in M.P.E.P § 2142, in order to establish a *prima facie* case of obviousness, three criteria must be met, *i.e.*, (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art references must teach or suggest all the claim limitations. The cited references, alone or in combination, fail to satisfy these requirements for a case of obviousness.

Boursnell et al., the primary references, disclose a list of a very great number of immunomodulating polypeptides, such as cytokines and chemokines, as well as complement components, immune system accessory/adhesion molecules and their respective receptors. Applicants note that IL-2, MIP-1α and MIP-1β are cited along with more than 40 other immunomodulating polypeptides (*see* column 7 lines 1-14 of Boursnell et al). In order for the skilled artisan to select the specification combination of IL-2 and MIP-1β, they would have to choose this combination out of more than 780 possibilities. No motivation is provided to the skilled artisan to choose the combination of the presently claimed invention. Although specific combinations of immunomodulating polypeptides are mentioned, specific reference is made to

combinations of cytokines (*i.e.*, more than one cytokine) and combinations of cytokines and accessory/adhesion molecules (*see* column 7 lines 23-26). Combinations involving IL-2, GM-CSF, lymphotactin and/or CD4OL are specifically disclosed (*see* column 8 lines 55-57). Thus, the skilled artisan would be led to chose the specifically combinations disclosed by the cited reference, rather than those of the claimed invention.

The first secondary reference, Hobart et al., fails to remedy the deficiencies of Boursnell et al. Hobart et al. disclose a method of treating solid tumors, relying on the administration of a plasmid DNA encoding IL-2 formulated with a cationic lipid mixture. Tumor volume was significantly reduced and survival rates enhanced in the IL-2 DNA-lipid treated group.

The other secondary reference, Nakashima at al., also fails to remedy the deficiencies of the first two cited references. Nakashima et al. discloses a method of treating tumors relying on the administration of a plasmid DNA encoding M1P-1α. Mice vaccinated with tumor cells transfected with the MIP-1α encoding plasmid show less tumor incidence in the inoculation site as compared to animals injected with non-transfected cells or IL-8-expressing cells. However, no significant difference was observed between the control groups and the MIP-1α treated groups with respect to the incidence rates of spontaneous lung metastases.

Thus, none of the cited references, either alone or in combination, provide any suggestion or motivation to associate the action of IL-2 with that of a MIP-1β chemokine in a vector composition. Further, none of these references disclose or even suggest a vector carrying a nucleic acid sequences encoding both IL-2 and a MIP-1β chemokine.

With regard to new claims 33-40, directed to a method of treating a proliferative disease, Applicants submit that the cited references do not apply. The skilled artisan would not have been motivated to combine the teaching of the cited references to arrive at the claims invention set forth in new claims 33-40, because none of the cited references, alone or in combination, contain any indication that a composition, and much less a treatment associating IL-2 with a MIP chemokine, would result in an anti-tumor response.

Boursnell et al., the primary reference, does not provide an enabled disclosure with respect to the presently claimed combination. Boursnell et al. disclose other combinations of immunomodulating polypeptides which do not include IL-2 and MIP. Boursnell et al. also fail to provide any incentive for the skilled artisan to combine IL-2 with a MIP chemokine from the lengthy list of immunomodulating polypeptides suitable for anti-tumor effect provided by Boursnell et al., because, as noted above, this combination is merely one possibility out of more than 780 others.

Hobart et al. fails to provide a disclosure or suggestion to combine the IL-2 encoding plasmid with a nucleic acid sequence which codes for a MIP chemokine. Nakashima at al. also fail to suggest or disclose the combination of IL-2 with a MIP chemokine. Moreover, Nakashima et al. would also not have provided a basis for a reasonable expectation of success because it is observed that a tumor cell line engineered to express a cytokine (IL-B) fail to provide any tumor reduction in vaccinated animals.

Therefore, Applicants submit that the cited references contain no suggestion to combine the teachings of the cited references to arrive at the claimed method of treatment using nucleic acid sequences encoding both IL-2 and a MIP chemokine.

Claims 1, 11, 13, 15 and 26 stand rejected under 35 USC § 103(a) as allegedly being unpatentable over Boursnell et al. (U.S. Patent No. 6,287,557) taken with Hobart et al, (U.S. Patent No. 5,147,055) and Nakashima at al, (*Phar. Res* 13:1896-1901 (1996)), in further view of Bruder et al. (U.S. Patent No. 6,440,944). The references are applied as above, and Bruder et al. is cited for purportedly disclosing defective recombinant adenoviral vectors.

Bruder et al. fail to remedy the deficiencies of the other three cited references. Bruder et al. fails to teach or ever to suggest recombinant adenoviral vector engineered to express both IL-2 and a MIP-Iβ chemokine. Therefore, Boursnell et al., Hobart et al., Nakashima et al. and Bruder et al., alone or in combination, fail to disclose or to suggest the claimed compositions and vectors directed to nucleic acid sequences encoding both IL-2 and a MIP-1β chemokine, as used in anti-tumor and anti-virus therapies.

Claims 14, 15, 31 and 32 stand rejected under 35 USC § 103(a) as purportedly unpatentable over Boursnell et al. (U.S. Patent No. 6,287,557) taken with Hobart et al. (U.S. Patent No. 5,147,055) and Nakashima et al. (*Phar. Res* 13:1896-1901 (1996)), in further view of Gruber et al. (U.S. Patent No. 6,410,326). The references are cited as set forth above, and Gruber et al. is cited for purportedly disclosing recombinant vaccinia virus vectors.

Gruber et al. fails to remedy the deficiencies of the other cited references, as discussed above. Gruber at al. fails to disclose or even to suggest recombinant vaccinia virus vectors engineered to express both IL-2 and a MIP-1 chemokine. Therefore, Boursnell et al., Hobart et al., Nakashima et al. and Gruber et al., alone or

in combination, fail to teach or suggest the claimed compositions and vectors involving nucleic acid sequences encoding both IL-2 and a MIP-1 chemokine, to be used in anti-tumor and anti-virus therapies.

In light of the above remarks, Applicants respectfully request that the rejections pursuant to 35 U.S.C. § 103 be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

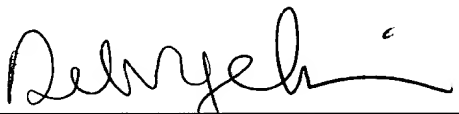
In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

In the event any further fees are due to maintain pendency of this application, the Examiner is authorized to charge such fees to Deposit Account No. 02-4800.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: May 17, 2004

By: 

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